

ORIGINAL INVESTIGATIONS

Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention



The Multicenter Randomized Controlled PRECISE-IVUS Trial

Kenichi Tsujita, MD, PhD,* Seigo Sugiyama, MD, PhD,† Hitoshi Sumida, MD, PhD,‡ Hideki Shimomura, MD, PhD,§ Takuro Yamashita, MD, PhD,|| Kenshi Yamanaga, MD,* Naohiro Komura, MD, PhD,* Kenji Sakamoto, MD, PhD,* Hideki Oka, MD, PhD,¶ Koichi Nakao, MD, PhD,# Sunao Nakamura, MD, PhD,** Masaharu Ishihara, MD, PhD,†† Kunihiko Matsui, MD, PhD,‡‡ Naritsugu Sakaino, MD, PhD,§§ Natsuki Nakamura, MD, PhD,||| Nobuyasu Yamamoto, MD, PhD,¶¶ Shunichi Koide, MD, PhD,## Toshiyuki Matsumura, MD, PhD,*** Kazuteru Fujimoto, MD, PhD,††† Ryusuke Tsunoda, MD, PhD,‡‡‡ Yasuhiro Morikami, MD, PhD,§§§ Koushi Matsuyama, MD, PhD,|| Shuichi Oshima, MD, PhD,‡ Koichi Kaikita, MD, PhD,* Seiji Hokimoto, MD, PhD,* Hisao Ogawa, MD, PhD,*||| for the PRECISE-IVUS Investigators

ABSTRACT

BACKGROUND Despite standard statin therapy, a majority of patients retain a high “residual risk” of cardiovascular events.

OBJECTIVES The aim of this study was to evaluate the effects of ezetimibe plus atorvastatin versus atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent percutaneous coronary intervention (PCI).

METHODS This trial was a prospective, randomized, controlled, multicenter study. Eligible patients who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily. Atorvastatin was uptitrated with a treatment goal of low-density lipoprotein cholesterol (LDL-C) <70 mg/dl. Serial volumetric intravascular ultrasound was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients.

RESULTS The combination of atorvastatin/ezetimibe resulted in lower levels of LDL-C than atorvastatin monotherapy (63.2 ± 16.3 mg/dl vs. 73.3 ± 20.3 mg/dl; $p < 0.001$). For the absolute change in percent atheroma volume (PAV), the mean difference between the 2 groups (-1.538% ; 95% confidence interval [CI]: -3.079% to 0.003%) did not exceed the pre-defined noninferiority margin of 3%, but the absolute change in PAV did show superiority for the dual lipid-lowering strategy (-1.4% ; 95% CI: -3.4% to -0.1% vs. -0.3% ; 95% CI: -1.9% to 0.9% with atorvastatin alone; $p = 0.001$). For PAV, a significantly greater percentage of patients who received atorvastatin/ezetimibe showed coronary plaque regression (78% vs. 58%; $p = 0.004$). Both strategies had acceptable side effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

CONCLUSIONS Compared with standard statin monotherapy, the combination of statin plus ezetimibe showed greater coronary plaque regression, which might be attributed to cholesterol absorption inhibition-induced aggressive lipid lowering. (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound [PRECISE-IVUS]; [NCT01043380](https://clinicaltrials.gov/ct2/show/study/NCT01043380)) (J Am Coll Cardiol 2015;66:495-507) © 2015 by the American College of Cardiology Foundation.



ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ACS = acute coronary syndrome(s)

AHA = American Heart Association

CAD = coronary artery disease

CSA = cross-sectional area

CV = cardiovascular

EEM = external elastic membrane

HDL-C = high-density lipoprotein cholesterol

IVUS = intravascular ultrasound

L = atorvastatin alone group

LDL-C = low-density lipoprotein cholesterol

LZ = atorvastatin plus ezetimibe group

PAV = percent atheroma volume

PCI = percutaneous coronary intervention

SAP = stable angina pectoris

TAV = total atheroma volume

Pivotal large-scale clinical trials of secondary preventive measures in patients with coronary artery disease (CAD) have shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce cardiovascular (CV) events and atherogenic lipoproteins (e.g., low-density lipoprotein cholesterol [LDL-C]) (1-3). The latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines focus on a healthy lifestyle together with a higher dose of statins without titration to a specific LDL-C target, which eliminates the need for additional medications (4). However, despite the current trend of aggressive lipid-lowering strategies, the majority of patients continue to experience CV events and remain exposed to high “residual risk” of future acute CV events. Therefore, additional novel pharmacologic strategies for the prevention of additional CV events risk remain essential, particularly for high-risk atherosclerotic CV disease patients (e.g., patients with diabetes, familial hypercholesterolemia, or acute coronary syndrome [ACS]).

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In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) investigators compared simvastatin with a placebo or simvastatin with ezetimibe (5). Both drugs reduce LDL-C levels, but in different ways: simvastatin blocks hepatic

cholesterol synthesis, whereas ezetimibe reduces cholesterol absorption through inhibition of the Niemann-Pick C1-like1 protein. Compared with simvastatin with a placebo, simvastatin plus 10 mg of ezetimibe daily led to a significantly lower incidence of the primary combined CV endpoint (CV death, myocardial infarction, rehospitalization for unstable angina, coronary revascularization, or stroke; 34.7% vs. 32.7%; $p = 0.016$) (6). This was the first trial to demonstrate the incremental clinical benefit of adding a nonstatin agent to standard statin therapy. However, whether the additional LDL-C lowering achieved when adding ezetimibe to statin therapy will lead to stronger coronary plaque regression is currently unknown. Also, it is not well understood whether using a dual lipid-lowering strategy (sole inhibition of cholesterol synthesis vs. combined inhibition of synthesis and absorption) affects plaque progression and/or regression. Thus, the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial was designed to evaluate the effects of ezetimibe added to atorvastatin, compared with atorvastatin monotherapy, on coronary plaque regression and a change in the lipid profile in patients with CAD.

METHODS

PRECISE-IVUS was a prospective, randomized, controlled, assessor-blind, multicenter study to evaluate the effect of ezetimibe added to atorvastatin on coronary artery atheroma volume as measured by

From the *Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; †Diabetes Care Center, Cardiovascular Division, Jinnouchi Hospital, Kumamoto, Japan; ‡Division of Cardiology, Kumamoto Central Hospital, Kumamoto, Japan; §Department of Cardiovascular Medicine, Fukuoka Tokushukai Medical Center, Kasuga, Japan; ||Division of Cardiology, Social Insurance Omuta Tenryo Hospital, Omuta, Japan; ¶Division of Cardiology, Health Insurance Hitoyoshi General Hospital, Hitoyoshi, Japan; #Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto, Japan; **Interventional Cardiology Unit, New Tokyo Hospital, Matsudo, Japan; ††Division of Coronary Artery Disease, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan; †††Department of Community Medicine, Kumamoto University, Kumamoto, Japan; §§Division of Cardiology, Amakusa Medical Center, Amakusa, Japan; |||Division of Cardiology, Shin-Beppu Hospital, Beppu, Japan; ¶¶Division of Cardiology, Miyazaki Prefectural Nobeoka Hospital, Nobeoka, Japan; ##Division of Cardiology, Health Insurance Kumamoto General Hospital, Yatsushiro, Japan; ***Division of Cardiology, Japan Labor Health and Welfare Organization Kumamoto Rosai Hospital, Yatsushiro, Japan; ††††Department of Cardiology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan; †††††Division of Cardiology, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan; §§§Division of Cardiology, Kumamoto City Hospital, Kumamoto, Japan; and the |||||Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan. This work was supported in part by a Grant-in-Aid for Young Scientists B (22790713, 24790769) and a Grant-in-aid for Scientific Research C (26461075) from the Ministry of Education, Science, and Culture, Japan (to Dr. Tsujita). Dr. Ogawa has received remuneration for lectures from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer, and Takeda; has received trust research/joint research funds from Bayer, Daiichi-Sankyo, and Novartis; and has received scholarship funds from AstraZeneca, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Dainippon Sumitomo Pharma, Kowa, MSD, Otsuka, Pfizer, Sanofi, Shionogi, and Takeda. Dr. Ishihara has received remuneration for lectures from MSD. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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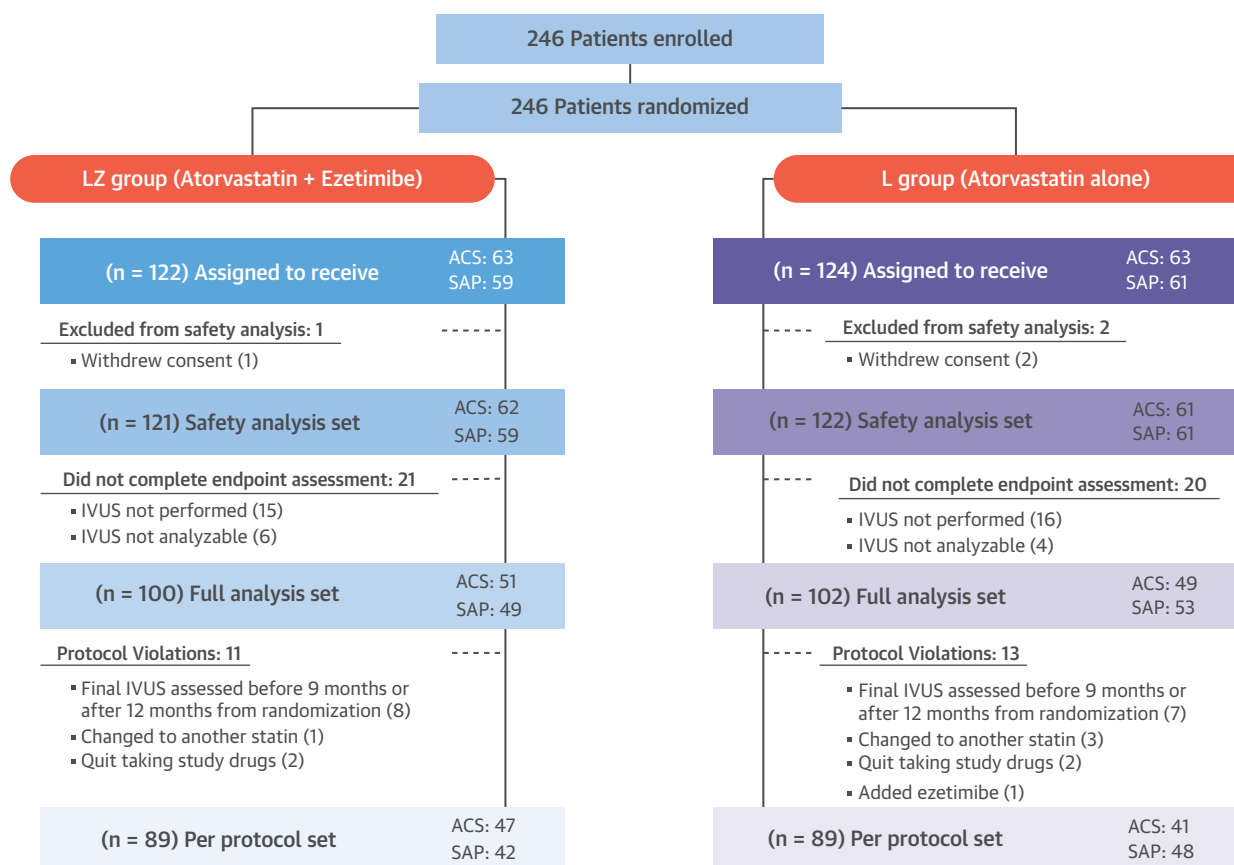
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intravascular ultrasound (IVUS) in patients with CAD. A detailed protocol of the PRECISE-IVUS trial was described previously (7). The study complied with the Declaration of the Helsinki with respect to investigation in humans, was approved by institutional review committees, and conducted in accordance with the guidelines of the ethics committee at participating institutions. Written informed consent was obtained from all patients.

Patients 30 to 85 years of age with CAD who satisfied all criteria for inclusion were enrolled after having undergone successful coronary angiography or percutaneous coronary intervention (PCI) under IVUS guidance to treat ACS or stable angina pectoris (SAP). Participants were required to have an LDL-C level at entry of >100 mg/dl. Eligible patients gave written informed consent, and then were randomly assigned in a 1:1 ratio to receive either atorvastatin (Lipitor, Pfizer, New York, New York) alone (L group) or

atorvastatin plus ezetimibe (Zetia, Merck, Whitehouse Station, New Jersey) 10 mg/day (LZ group) using a web-based randomization software (Figure 1). Randomization was stratified by: 1) sex; 2) age; 3) history of hypertension; 4) history of diabetes; 5) history of peripheral arterial disease; 6) serum LDL-C level; 7) serum high-density lipoprotein cholesterol (HDL-C) level; 8) serum triglyceride level; and 9) statin pretreatment before study enrollment. Atorvastatin was increased by titration within the usual dose range with a treatment goal of LDL-C <70 mg/dl on the basis of published lipoprotein management guidelines (8). Lipid profiles and other biomarker levels were measured at baseline and follow-up at 9 to 12 months (analyzed by SRL Co., Ltd., Tokyo, Japan) at participating institutions or general physician clinics that conducted medical examinations and blood testing. Participating clinicians were asked to continue administration of the allocated drugs in accordance

FIGURE 1 Flow Chart



Patients were randomized by treatment group and also followed by presentation. ACS = acute coronary syndrome(s); IVUS = intravascular ultrasound; L = atorvastatin alone group; LZ = atorvastatin plus ezetimibe group; SAP = stable angina pectoris.

with the previously described randomization and titration protocol until the study's end. Serial IVUS and coronary angiography were performed at baseline and again at 9- to 12-month follow-up at participating CV centers. Safety was monitored throughout the study and evaluated by periodic medical examination and laboratory tests at 3, 6, and 9 to 12 months after enrollment.

IVUS IMAGE ACQUISITION AND ANALYSIS. PRECISE-IVUS used IVUS imaging to trace the lumen and vessel border (external elastic membrane [EEM]) and to evaluate coronary atheroma progression and/or regression. Investigators were required to use the same IVUS imaging system for both baseline and follow-up IVUS image acquisition. The IVUS catheter was advanced into a PCI or non-PCI vessel as far distally possible to safely reach to obtain the longest possible target segment for analysis, and it was then withdrawn at a pull-back speed of 0.5 mm/s automatically after intracoronary administration of nitroglycerin 0.1 to 0.2 mg. IVUS studies were archived onto CD-ROMs or DVDs with study-specific identification numbers on an anonymous basis and sent to an independent, treatment-allocation-blinded IVUS core laboratory at the Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University. The IVUS analysis was performed by 2 independent experienced observers (K.T. and K.S.) who were unaware of the treatment allocation and temporal sequence of paired images according to consensus standards (9). Baseline and follow-up IVUS images were reviewed together on a display, and target vessels and segments were selected on the basis of the previously described IVUS inclusion and/or exclusion criteria (7). Specifically, the operator selected a target segment in both the longest and least angulated segment that met the inclusion criteria among the PCI or non-PCI vessels. The target segment to be monitored was determined in a non-PCI site (>5 mm proximal or distal to the PCI site) with a reproducible fiducial index, usually a side branch, as the beginning and endpoint of the segments to be analyzed. Patients who met pre-specified requirements for IVUS image quality were then eligible for the full analysis set. Coronary atheroma parameters of the selected target segment were assessed by volumetric analysis with the echoPlaque3 system (INDEC Systems, Inc., Mountain View, California). Intra- and interobserver reproducibilities for measuring the primary efficacy endpoint by 2 independent IVUS analysts were assessed in 50 randomly selected plaques. The correlation coefficient and mean difference \pm SD were 0.999 and $0.002 \pm 0.121\%$ (of the absolute mean

value; $-1.379 \pm 2.473\%$, of the samples) for intra-observer variability and 0.981 and $0.015 \pm 0.474\%$ for interobserver variability, with good agreement between analysts.

On the basis of expert consensus (9), the primary efficacy endpoint was the absolute change in percent atheroma volume (PAV) of the coronary selected target segment from baseline to follow-up. The PAV was calculated as follows:

$$\text{PAV} = \frac{\Sigma (\text{EEM CSA} - \text{lumen CSA})}{\Sigma \text{EEM CSA}} \times 100$$

where EEM CSA is the cross-sectional area of the EEM border, and the lumen CSA is the cross-sectional area of the lumen border. For PAV, the summation of the EEM CSA minus the lumen CSA was performed first. This value was then divided by the summation of the EEM CSA, which was finally multiplied by 100. The absolute change in PAV was calculated as the PAV at 9- to 12-month follow-up minus the PAV at baseline. The secondary efficacy endpoint was percent change in normalized total atheroma volume (TAV), which was calculated as follows:

$$\text{TAV}_{\text{normalized}} = \frac{\Sigma (\text{EEM CSA} - \text{lumen CSA})}{\text{no. of analyzed frames per patients} \times \text{median number of analyzed frames in the population}}$$

For TAV, the summation of the EEM CSA minus the lumen CSA was performed first. This value was divided by the number of analyzed frames in the pullback and then multiplied by the median number of analyzed frames in the study population. The average plaque area in the pullback was multiplied by the median number of images analyzed in the entire cohort to compensate for differences in segment length between subjects.

BIOMARKER ASSESSMENT. The secondary endpoints included absolute and percent changes in the lipid, glycemic, and inflammatory profile [total cholesterol, LDL-C, triglyceride, HDL-C, HDL₂-C, HDL₃-C, malondialdehyde-modified LDL-C, remnant-like lipoprotein particle cholesterol, small-dense LDL-C, free-fatty acid, apolipoprotein A-I, apolipoprotein B, apolipoprotein C-II, apolipoprotein C-III, lipoprotein(a), fasting insulin level, glycosylated hemoglobin, adiponectin, lathosterol, cholestanol, sitosterol, campesterol, and high-sensitivity C-reactive protein] during the study period.

STATISTICAL ANALYSIS. Statistical analysis was performed using SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, New York). After the descriptive statistics, continuous variables (mean \pm SD

and medians with interquartile ranges) between the 2 groups were compared using the unpaired Student *t* test or the Mann-Whitney U test. Continuous variables between the baseline and follow-up were compared by 1-sample Student *t* tests or the Wilcoxon signed rank test according to their distributions. Categorical variables (frequencies) were compared using chi-square statistics or the Fisher exact test. The relationships between the absolute change in PAV and several factors, including follow-up LDL-C level and the cholesterol absorption marker, were evaluated with a simple regression analysis. The full analysis dataset, in which the patients had measurable IVUS images both at baseline

and at follow-up, was used for the primary analyses. The per-protocol dataset analysis was also specified if the enrolled patients completely met the inclusion and exclusion criteria and were followed according to protocol. If patients received the study drugs at least once, they were included in the safety analysis. The number of adverse events was assessed to determine safety profiles. A *p* value <0.05 was considered significant.

The PRECISE-IVUS trial aimed to evaluate whether the effect of atorvastatin/ezetimibe on coronary atheroma regression would not be inferior to that of atorvastatin monotherapy. A detailed structure of statistical analyses in the present study was described

TABLE 1 Clinical Demographics Between Groups

	Full Study Cohort		ACS Cohort		SAP Cohort	
	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 51)	L Group (n = 49)	LZ Group (n = 49)	L Group (n = 53)
Age, yrs	66 ± 10	67 ± 10	64 ± 11	65 ± 10	67 ± 8	68 ± 10
Male	78 (78)	80 (78)	41 (80)	41 (84)	37 (76)	39 (74)
Weight, kg	67.1 ± 13.2	65.7 ± 10.8	68.3 ± 13.6	67.0 ± 12.1	65.8 ± 12.8	64.6 ± 9.5
Body mass index, kg/m ²	24.8 ± 3.4	24.9 ± 3.1	24.9 ± 3.5	24.8 ± 3.0	24.6 ± 3.3	25.1 ± 3.2
Hypertension	75 (75)	67 (66)	38 (75)	28 (57)	37 (76)	39 (74)
Diabetes mellitus						
Insulin	4 (4)	4 (4)	1 (2)	2 (4)	3 (6)	2 (4)
Noninsulin	25 (25)	27 (26)	11 (22)	11 (22)	14 (29)	16 (30)
HbA _{1c} , %	5.4 (5.1-6.2)	5.5 (5.3-6.3)	5.3 (5.2-6.0)	5.6 (5.3-6.3)	5.6 (5.2-6.4)	5.5 (5.3-6.3)
Dyslipidemia	72 (72)	70 (69)	33 (65)	37 (76)	39 (80)	33 (62)
Current smoking	20 (20)	33 (32)	13 (25)	22 (45)	7 (14)	11 (21)
Presentation of ACS						
STEMI			26 (51)	25 (51)		
NSTEMI	N/A	N/A	5 (10)	7 (14)	N/A	N/A
Unstable angina			20 (39)	17 (35)		
History of PCI	19 (19)	15 (15)	3 (6)	5 (10)	16 (33)	10 (19)
History of CABG	0	0	0	0	0	0
History of MI	15 (15)	13 (13)	4 (8)	4 (8)	11 (22)	9 (17)
History of stroke	10 (10)*	1 (1)	4 (8)	1 (2)	6 (12)*	0
History of PAD	3 (3)	4 (4)	1 (2)	1 (2)	2 (4)	3 (6)
Previous statin use	46 (46)	49 (48)	22 (43)	26 (53)	24 (49)	23 (43)
Concomitant medication						
Aspirin	100 (100)	102 (100)	51 (100)	49 (100)	49 (100)	53 (100)
Thienopyridines†	100 (100)	101 (99)	51 (100)	48 (98)	49 (100)	53 (100)
Cilostazol	1 (1)	0	0	0	1 (2)	0
Sarpogrelate hydrochloride	2 (2)	2 (2)	1 (2)	1 (2)	1 (2)	1 (2)
Warfarin	5 (5)	1 (1)	4 (8)	0	1 (2)	1 (2)
Nitrates	6 (6)	14 (14)	5 (10)	4 (8)	1 (2)†	10 (19)
Beta-blockers	41 (41)	51 (50)	29 (57)	29 (59)	12 (24)	22 (42)
Calcium blockers	44 (44)	35 (34)	21 (41)	11 (22)	23 (47)	24 (45)
ACE inhibitors	25 (25)	28 (27)	17 (33)	19 (39)	8 (16)	9 (17)
ARBs	48 (48)	37 (36)	23 (45)	13 (27)	25 (51)	24 (45)
Stomach medicines	89 (89)	89 (87)	49 (96)	45 (92)	40 (82)	44 (83)
Hypoglycemic agents	25 (25)	25 (25)	9 (18)	11 (22)	16 (33)	14 (26)

Values are mean ± SD, n (%), or median (interquartile range [IQR]). *The significant between-group difference with a *p* <0.05. †Clopidogrel, prasugrel, and ticlopidine.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome(s); ARB = angiotensin II receptor blocker; CABG = coronary artery bypass grafting; HbA_{1c} = glycosylated hemoglobin; L = atorvastatin alone; LZ = atorvastatin/ezetimibe; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SAP = stable angina pectoris; STEMI = ST-segment elevation myocardial infarction.

elsewhere (7). According to the pre-specified non-inferiority margin and sample size calculation, investigators established a noninferiority margin of 3%, and calculated that 100 subjects were needed in each group, with an alpha level of 5% that gave power of 80%. A key secondary objective was to determine whether the atorvastatin/ezetimibe combination was superior to atorvastatin monotherapy with respect to the nominal change in coronary PAV.

RESULTS

From June 21, 2010, through April 22, 2013, a total of 246 patients were enrolled at 17 CV centers in Japan and randomly assigned to receive atorvastatin plus ezetimibe 10 mg/day (n = 122) or atorvastatin alone (n = 124) (Figure 1). After 9 to 12 months of treatment, 202 patients (82%) remained for follow-up and underwent repeat IVUS imaging. Of these patients, 100 were in the LZ group and 102 in the L group. The LZ group experienced a slightly longer follow-up period (10.1 ± 1.8 months vs. 9.7 ± 1.7 months; $p = 0.10$).

There were no significant differences in demographic characteristics or baseline medication use

between the 2 treatment groups, except for history of stroke and frequency of nitrate use (Table 1). PRECISE-IVUS investigators enrolled patients with both ACS and SAP; eventually, one-half of the study patients were assigned to the ACS cohort; the others to the SAP cohort. The majority of patients (78%) were men, and 30% of the total study patients had diabetes. Among those with ACS, the clinical presentation was ST-segment elevation myocardial infarction in 51%. In terms of concomitant medication, the majority of patients were treated with optimal medical therapy in addition to lipid-lowering study drugs.

Baseline and follow-up laboratory data are shown in Table 2. Although LDL-C levels were similar between the 2 groups at baseline, LDL-C level was significantly lower at 9 to 12 months in the LZ group than in the L group ($p < 0.001$), and the dual lipid-lowering strategy showed more remarkable reduction of LDL-C level than atorvastatin monotherapy during the study ($p < 0.001$). These values resulted in the LZ group experiencing a lower ratio of LDL-C to HDL-C during treatment (1.45 ± 0.45 vs. 1.77 ± 0.55 ; $p < 0.001$) and having a greater proportion of patients who achieved LDL-C levels <70 mg/dl (72% vs. 47%; $p = 0.001$) compared

TABLE 2 Baseline and Follow-Up Laboratory Data

	Baseline		Follow-Up		Percent Change (%)		p Value
	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 100)	L Group (n = 102)	
TC, mg/dl	177.3 \pm 32.4	172.7 \pm 32.6	129.4 \pm 22.0	138.7 \pm 26.2	-25 \pm 17	-18 \pm 18	0.006
HDL-C, mg/dl	41.1 \pm 9.5	40.0 \pm 10.3	45.6 \pm 11.9	43.3 \pm 11.5	14 \pm 26	11 \pm 25	0.5
LDL-C, mg/dl	109.8 \pm 25.4	108.3 \pm 26.3	63.2 \pm 16.3	73.3 \pm 20.3	-40 \pm 18	-29 \pm 24	<0.001
Triglycerides, mg/dl	114 (81 to 158)	116 (92 to 159)	92 (76 to 120)	111 (87 to 139)	-14 (-33 to 18)	-9 (-33 to 25)	0.3
Lipoprotein (a), mg/dl	21.5 (12.5 to 37.5)	18.0 (10.0 to 30.5)	17.0 (8.0 to 36.0)	14.0 (7.0 to 30.5)	-12 (-42 to 17)	-20 (-50 to 7)	0.1
Apolipoprotein A-I, mg/dl	112.8 \pm 20.2	112.6 \pm 21.6	128.1 \pm 25.0	123.7 \pm 24.5	15 \pm 21	11 \pm 17	0.2
Apolipoprotein B, mg/dl	96.9 \pm 20.6	94.0 \pm 19.2	62.5 \pm 13.0	69.0 \pm 16.1	-34 \pm 16	-26 \pm 20	0.001
Free fatty acid, μ Eq/l	402 (281 to 574)	431 (278 to 610)	384 (218 to 541)	376 (223 to 627)	-7 (-50 to 59)	-11 (-56 to 68)	0.8
MDA-LDL, U/l	122.9 \pm 39.9	121.8 \pm 40.5	81.8 \pm 24.1	95.1 \pm 30.8	-27.7 \pm 27.0	-15.3 \pm 38.5	0.1
RLP-C, mg/dl	3.8 (2.7 to 4.8)	3.5 (2.7 to 5.1)	2.6 (2.1 to 3.5)	3.1 (2.4 to 4.5)	-28 (-48 to 3)	-17 (-37 to 17)	0.02
sdLDL-C, mg/dl	32.7 \pm 15.6	30.5 \pm 11.8	20.6 \pm 8.6	22.5 \pm 10.1	-28.5 \pm 33.5	-21.4 \pm 35.0	0.2
Insulin, μ U/ml	6.8 (4.3 to 10.1)	7.3 (4.9 to 9.6)	7.9 (4.9 to 12.6)	8.4 (5.4 to 12.5)	15 (-33 to 73)	22 (-18 to 51)	0.99
HbA _{1c} , %	5.4 (5.1 to 6.3)	5.5 (5.3 to 6.3)	5.6 (5.2 to 6.0)	5.7 (5.4 to 6.1)	3 (-2 to 5)	2 (-4 to 4)	0.2
Total adiponectin, μ g/ml	4.7 (3.4 to 7.0)	4.1 (2.7 to 5.7)	6.2 (3.9 to 8.3)	5.0 (3.3 to 7.2)	28 (-4 to 64)	19 (-5 to 63)	0.4
HMW adiponectin, μ g/ml	1.9 (1.0 to 3.1)	1.4 (0.8 to 2.6)	2.3 (1.2 to 4.3)	1.6 (0.9 to 2.9)	24 (-25 to 74)	19 (-25 to 86)	0.9
Lathosterol, μ g/ml	1.1 (0.7 to 2.3)	1.3 (0.7 to 2.1)	1.0 (0.8 to 1.4)	0.6 (0.4 to 0.9)	-15 (-53 to 45)	-53 (-71 to -22)	<0.001
Campesterol, μ g/ml	4.4 (3.3 to 5.7)	3.7 (2.8 to 5.0)	2.3 (1.8 to 2.9)	4.9 (3.5 to 6.4)	-46 (-61 to -30)	22 (-5 to 61)	<0.001
Sitosterol, μ g/ml	2.2 (1.7 to 3.0)	2.0 (1.5 to 2.7)	1.3 (1.0 to 1.9)	2.4 (1.8 to 3.4)	-39 (-53 to -20)	31 (-6 to 67)	<0.001
Lathosterol, μ g/100 mg TC	68 (43 to 109)	73 (44 to 116)	81 (59 to 108)	49 (33 to 66)	14 (-28 to 68)	-36 (-57 to 2)	<0.001
Campesterol, μ g/100 mg TC	252 (199 to 321)	215 (165 to 281)	183 (143 to 228)	362 (258 to 451)	-30 (-43 to -10)	53 (24 to 82)	<0.001
Sitosterol, μ g/100 mg TC	129 (98 to 174)	113 (91 to 152)	101 (78 to 145)	178 (131 to 264)	-15 (-34 to 9)	60 (27 to 106)	<0.001
Campesterol/lathosterol	3.7 (2.2 to 6.5)	2.8 (2.0 to 5.0)	2.2 (1.5 to 3.6)	7.5 (4.3 to 12.5)	-40 (-66 to 10)	167 (48 to 267)	<0.001
hs-CRP, mg/l	3.0 (1.0 to 14.9)	3.7 (1.2 to 8.1)	0.4 (0.2 to 1.3)	0.3 (0.2 to 0.8)	-89 (-97 to -59)	-86 (-95 to -70)	0.9

Values are mean \pm SD or median (IQR).

HDL-C = high-density lipoprotein cholesterol; HMW = high molecular weight; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MDA-LDL = malondialdehyde-modified LDL; RLP-C = remnant like particles cholesterol; sdLDL-C = small-dense LDL-C; TC = total cholesterol; other abbreviations as in Table 1.

TABLE 3 Demonstration of Coronary Plaque Progression/Regression

	Baseline			9-12 Months Follow-Up		
	LZ Group (n = 100)	L Group (n = 102)	p Value	LZ Group (n = 100)	L Group (n = 102)	p Value
Plaque volume, mm ³	72.6 (37.6 to 117.4)	76.3 (45.5 to 128.4)	0.5	69.6 (35.0 to 107.2)	77.3 (45.4 to 126.2)	0.2
Percent atheroma volume, %	51.3 ± 10.8	50.9 ± 11.4	0.8	49.3 ± 10.3	50.4 ± 11.6	0.5
TAV _{norm} , mm ³	89.6 (65.8 to 118.8)	84.8 (61.5 to 112.7)	0.7	85.4 (65.5 to 110.0)	87.2 (60.1 to 111.8)	0.6
Vessel volume, mm ³	144.4 (78.5 to 218.6)	159.8 (97.7 to 244.4)	0.3	141.8 (70.0 to 222.3)	155.7 (101.4 to 241.6)	0.2
Lumen volume, mm ³	70.4 (34.5 to 117.1)	79.4 (47.5 to 116.6)	0.3	65.8 (36.5 to 113.8)	79.1 (47.7 to 115.3)	0.2
Lesion length, mm	10.1 (5.6 to 14.6)	12.4 (7.5 to 16.0)	0.11	9.7 (5.8 to 14.5)	11.9 (7.2 to 15.9)	0.10
Absolute Change						
	LZ Group (n = 100)	p Value Compared With Baseline	L Group (n = 102)	p Value Compared With Baseline	p Value Between Groups	
Plaque volume, mm ³	-3.9 (-10.6 to 0.0)	<0.001	-1.0 (-6.8 to 5.7)	0.4	0.001	
Percent atheroma volume, %	-1.4 (-3.4 to -0.1)	<0.001	-0.3 (-1.9 to 0.9)	0.03	0.001	
ACS cohort	-2.3 (-3.7 to -0.5)	<0.001	-0.2 (-1.3 to 0.5)	0.2	<0.001	
SAP cohort	-1.2 (-2.2 to -0.1)	0.001	-0.7 (-2.3 to 1.1)	0.08	0.2	
TAV _{norm} , mm ³	-5.3 (-12.4 to 0.1)	<0.001	-1.2 (-5.7 to 3.3)	0.1	<0.001	
Vessel volume, mm ³	-4.1 (-12.6 to 3.1)	0.001	-0.6 (-11.8 to 10.6)	0.9	0.04	
Lumen volume, mm ³	-0.3 (-4.9 to 4.0)	0.4	0.8 (-5.6 to 6.9)	0.5	0.4	
Percent Change (%)						
	LZ Group (n = 100)	p Value Compared With Baseline	L Group (n = 102)	p Value Compared With Baseline	p Value Between Groups	
Plaque volume, mm ³	-5.2 (-15.1 to 0.0)	N/A	-1.3 (-8.6 to 6.5)	N/A	<0.001	
TAV _{norm} , mm ³	-6.6 (-12.6 to 0.2)	N/A	-1.4 (-6.7 to 4.4)	N/A	<0.001	
ACS cohort	-10.2 (-13.6 to -3.8)	N/A	-1.3 (-6.7 to 4.4)	N/A	<0.001	
SAP cohort	-5.0 (-10.3 to 1.2)	N/A	-1.5 (-6.3 to 4.0)	N/A	0.08	
Vessel volume, mm ³	-2.5 (-9.0 to 2.5)	N/A	-0.3 (-6.5 to 7.9)	N/A	0.04	
Lumen volume, mm ³	-0.6 (-7.2 to 7.4)	N/A	0.9 (-7.2 to 11.6)	N/A	0.4	
Values are median (IQR) or mean ± SD.						
TAV = total atheroma volume; other abbreviations as in Table 1 .						

with the L group. Although there was no difference between the 2 groups in percent change of high-sensitivity C-reactive protein, cholesterol absorption markers—campesterol, sitosterol, campesterol-to-cholesterol ratio, sitosterol-to-cholesterol ratio, and campesterol-to-lathosterol ratio—were all significantly decreased in the LZ group from baseline to 9 to 12 months of follow-up. Those levels were significantly increased in the L group.

IVUS ANALYSIS RESULTS. Table 3 shows the IVUS efficacy endpoints at each time point and the serial changes (Central Illustration). Analyses were performed on data from the full analysis set population (Figure 1); comparison of the primary endpoint was analyzed as part of hierarchical sequence testing (starting with testing of the primary endpoint for noninferiority, and then testing superiority) to control for the type I error. The primary endpoint (noninferiority of the LZ to the L group in absolute change in PAV) was proved (Figure 2), with a mean difference of drug effects on absolute change in PAV of -1.538% (95% confidence interval [CI]: -3.079% to 0.003%).

The upper limit of the 95% CI did not exceed the pre-defined noninferiority margin of 3% (7). For superiority, the absolute change in PAV decreased by -1.4% (-3.4% to -0.1%) in the LZ group and by -0.3% (-1.9% to 0.9%) in the L group ($p < 0.001$ for the change from baseline in the LZ group and $p = 0.03$ in the L group; $p = 0.001$ for the between-group comparison). For PAV, a significantly greater percentage of patients of the LZ group showed coronary plaque regression (78% vs. 58%; $p = 0.004$).

For percent change in TAV_{normalized}, a secondary IVUS endpoint, the effect was more favorable in the LZ group than in the L group (-6.6%; 95% CI: -12.6% to 0.2% vs. -1.4%; 95% CI: -6.7% to 4.4%; $p < 0.001$). For TAV_{normalized}, a significantly greater proportion of the LZ group patients had disease regression (75% vs. 58%; $p = 0.02$).

With regard to vessel remodeling during follow-up, the vessel volume of the target segment analyzed was negatively remodeled in the LZ group versus the L group, although the lumen volume serial change was comparable between the groups.

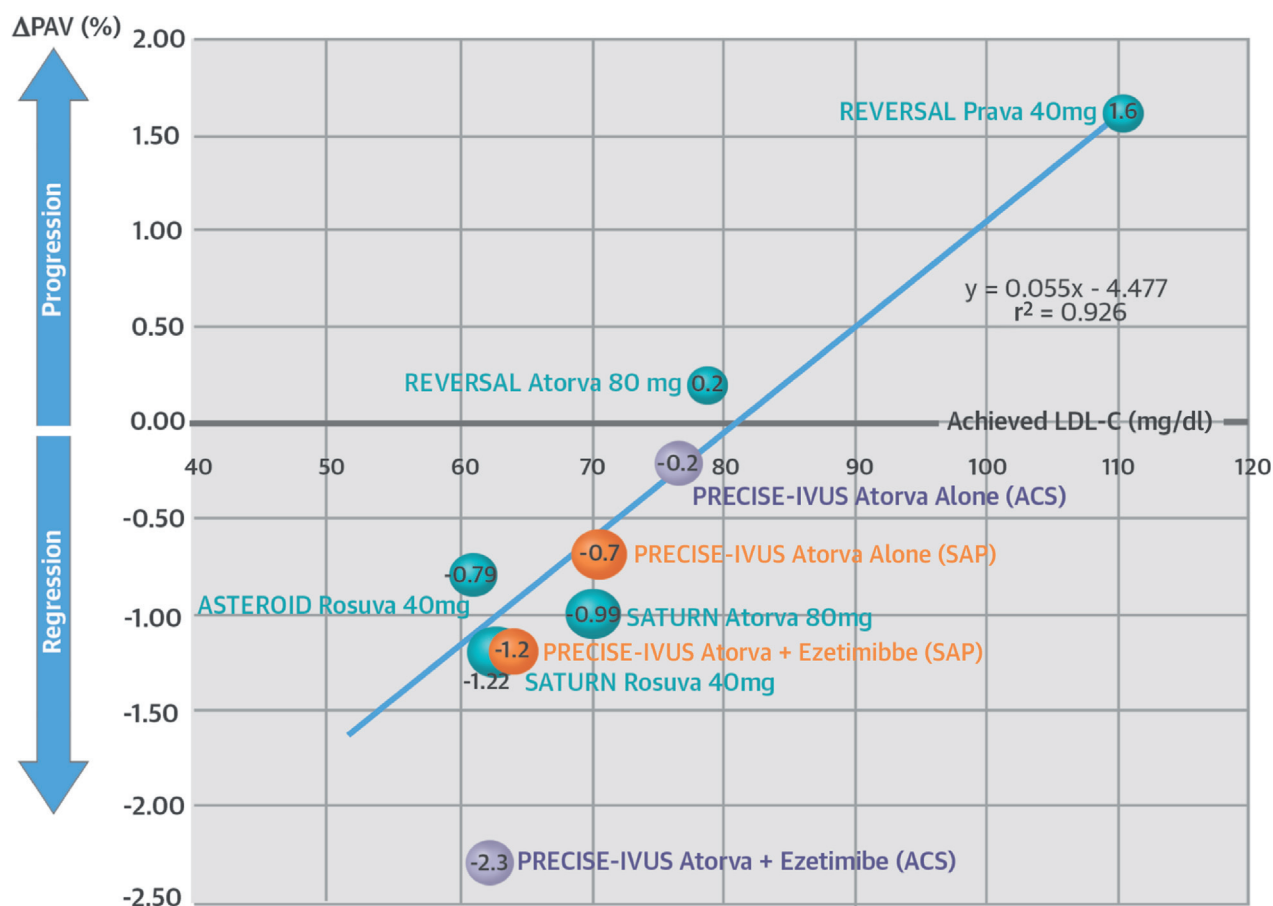
Similar results were confirmed even in the “per protocol set” cohort (Online Table 1).

After classifying the entire study cohort into either an ACS or SAP cohort, the between-group difference of the plaque regression effect (the more prominent plaque regression effect in the LZ group compared with the L group) was greater in the ACS cohort, in terms of both the absolute change in PAV and the percent change in TAV_{normalized}. This suggested that aggressive dual lipid-lowering with atorvastatin/ezetimibe might reverse the coronary plaque development

process in patients with ACS rather than with SAP (Central Illustration). Representative serial changes of the plaque progression and/or regression visualized by IVUS in both groups are shown in Figure 3.

Table 4 compares laboratory data between the patient groups with plaque regression versus progression in PAV. Compared with patients with plaque progression (any positive change in PAV), the achieved LDL-C level was significantly suppressed in patients with plaque regression (any negative change in PAV), as well as apolipoprotein B and small-dense

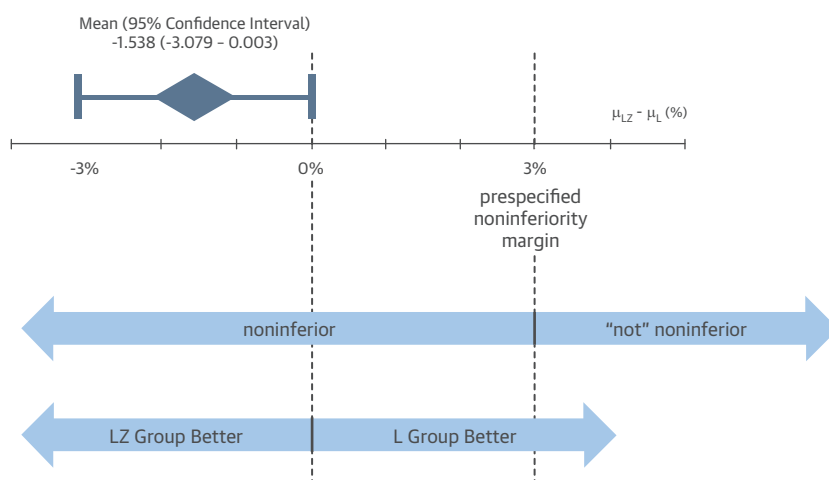
CENTRAL ILLUSTRATION Relationship Between Achieved Low-Density Lipoprotein Cholesterol Levels and the Median Change in Percent Atheroma Volume for Previous Intravascular Ultrasound Trials and the PRECISE-IVUS Trial



Tsujita, K. et al. J Am Coll Cardiol. 2015; 66(5):495-507.

There has been a close correlation between achieved low-density lipoprotein cholesterol (LDL-C) levels and the median change in percent atheroma volume in several intravascular ultrasound trials ($r^2 = 0.926$). Even in the stable angina pectoris cohort of the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial, these plots are located in range with the pre-existing regression line. In contrast, the plot is located far below the line in the atorvastatin/ezetimibe combination arm of the acute coronary syndrome cohort of the PRECISE-IVUS trial, whereas the plot was still in range with the line in the atorvastatin monotherapy arm. ACS = acute coronary syndrome(s); ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; Atorva = atorvastatin; ΔPAV = absolute change in percent atheroma volume; Prava = pravastatin; REVERSAL = Reversal of Atherosclerosis With Aggressive Lipid-Lowering; SAP = stable angina pectoris; SATURN = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin.

FIGURE 2 Primary Endpoint: Absolute Change in PAV

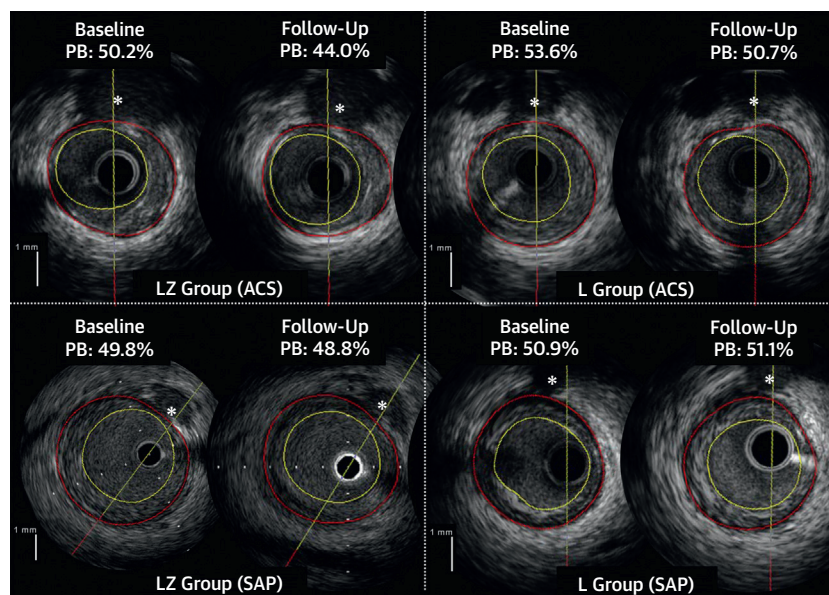


The atorvastatin/ezetimibe (LZ) group was noninferior to the atorvastatin-alone (L) group in terms of the primary endpoint, which was the absolute change in percent atheroma volume (PAV). $\mu_{LZ} - \mu_L$ indicates the difference of drug effects on absolute change in PAV, where μ_{LZ} represents the absolute change in PAV in the LZ group and μ_L represents that of the L group.

LDL-C. Among cholesterol absorption markers, the campesterol-to-cholesterol ratio tended to be lower in the regression group versus the progression group. As shown in [Figure 4](#), relationships between these

biomarkers and the absolute change in PAV were evaluated using linear regression analysis in the full study, ACS, and SAP cohorts. Similar to a recent IVUS study (10), there were no strong correlations between

FIGURE 3 Plaque Progression/Regression



IVUS images of the same cross sections at baseline and follow-up show outlined leading edges of lumen (yellow line) and external elastic membrane (red line). Note the substantial reduction in plaque area observed for the cross-sectional images, especially in the LZ group versus the L group. *Side branches show same position and shape. PB = plaque burden; other abbreviations as in [Figures 1 and 2](#).

TABLE 4 Comparison Between PAV Regression and Progression

	Regression in PAV (n = 135)	Progression in PAV (n = 67)	p Value
TC, mg/dl	130.6 ± 24.0	141.5 ± 24.3	0.006
HDL-C, mg/dl	44.0 ± 12.2	45.3 ± 10.7	0.2
LDL-C, mg/dl	65.5 ± 17.8	74.3 ± 20.3	0.003
Ratio of LDL-C/HDL-C	1.57 ± 0.51	1.71 ± 0.54	0.08
Triglycerides, mg/dl	95.0 (76.0-126.5)	102.0 (85.0-142.0)	0.2
Lipoprotein(a), mg/dl	15.0 (8.0-32.0)	16.0 (8.0-32.5)	0.8
Apolipoprotein A-I, mg/dl	124.0 ± 25.6	130.0 ± 22.6	0.04
Apolipoprotein B, mg/dl	64.1 ± 14.6	69.3 ± 15.2	0.02
Free fatty acid, μ Eq/l	393.0 (232.0-546.5)	329.0 (195.0-635.5)	0.2
MDA-LDL, U/l	86.9 ± 26.3	92.0 ± 32.4	0.4
RLP cholesterol, mg/dl	2.8 (2.2-3.7)	3.1 (2.4-4.7)	0.4
sdLDL cholesterol, mg/dl	20.4 ± 8.6	24.1 ± 10.6	0.02
Lathosterol, μ g/100 mg TC	63.5 (43.5-91.2)	57.7 (44.3-85.3)	0.8
Campesterol, μ g/100 mg TC	225.0 (174.4-356.9)	261.9 (207.1-395.8)	0.1
Sitosterol, μ g/100 mg TC	136.9 (93.2-189.8)	156.5 (104.3-206.2)	0.2
Campesterol/lathosterol	3.8 (2.0-7.6)	4.2 (2.8-8.0)	0.8

Values are mean ± SD or median (IQR).
PAV = percent atheroma volume; other abbreviations as in [Tables 1 and 2](#).

these biomarkers and absolute change in PAV. In the achieved LDL-C level at follow-up ([Figures 4A to 4C](#)) and the percent change in the campesterol-to-cholesterol ratio during follow-up ([Figures 4D to 4F](#)), despite the weak correlation, the steeper positive slope of the regression line was noted more in the ACS cohort than the SAP cohort, which suggested plaque development reversibility in patients with ACS.

[Online Table 2](#) shows the clinical events, laboratory abnormalities, and reasons for study drug discontinuation. Both strategies were well tolerated throughout the study. For both groups, the frequency of CV events was similar, the rate of abnormal laboratory values was low, and the rate of target lesion/vessel revascularization was similar.

DISCUSSION

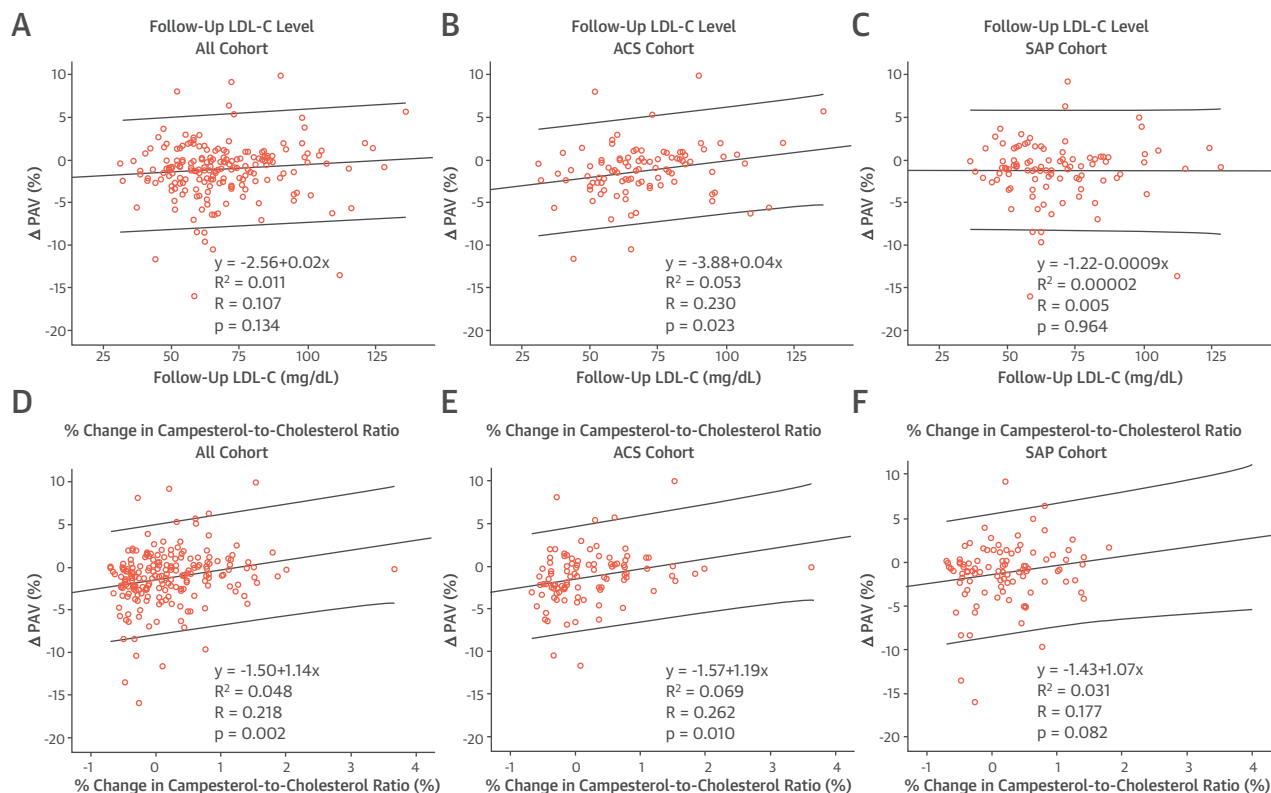
The major findings of PRECISE-IVUS include: 1) the dual lipid-lowering strategy that combined atorvastatin and ezetimibe resulted in a more remarkable reduction of LDL-C than atorvastatin monotherapy, with suppression of the compensatory enhancement of cholesterol absorption during 9 to 12 months of follow-up; 2) volumetric IVUS analysis demonstrated not only the noninferiority of the combination therapy in terms of absolute change in PAV, but also the superiority with regard to coronary plaque regression with negative vascular remodeling in the analyzed target segment; and 3) the significant favorable effect of the dual lipid-lowering strategy on the coronary atherosclerotic development was pronounced,

especially in the ACS cohort, along with a reduction of cholesterol absorption markers and lower LDL-C levels.

The large-scale clinical trials that evaluated combined statin/ezetimibe therapy did not necessarily generate positive results. In the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial ([11](#)), the simvastatin/ezetimibe combination failed to show a significant difference in intima-media thickness versus simvastatin alone. In addition, there were no differences in the preventive effect on major CV events in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, which was conducted in patients with aortic stenosis ([12](#)), whereas the SHARP (Study of Heart and Renal Protection) trial provided evidence for safe and effective lowering of LDL-C with a combination of simvastatin/ezetimibe in a wide range of patients with chronic kidney disease ([13](#)). However, when the “coronary ischemic events” specifically mentioned in the SEAS trial were examined, the combination of simvastatin/ezetimibe was significantly superior to placebo in terms of the preventive effect on ischemic heart disease ([12](#)). The IMPROVE-IT trial ([6](#)) was the first to demonstrate an incremental clinical benefit by adding a nonstatin agent to standard statin therapy, and proposed that the dual lipid-lowering strategy with statin/ezetimibe was a promising novel anti-atherosclerotic strategy in patients with residual risk. Compared with simvastatin plus placebo, simvastatin/ezetimibe reduced atherosclerotic CV events, namely, ischemic stroke by 21% and myocardial infarction by 13%, which led to a significantly lower incidence of the primary combined CV endpoint. In terms of the lipid profile in IMPROVE-IT trial participants, mean LDL-C was significantly lower in patients treated with simvastatin and ezetimibe relative to those treated with simvastatin monotherapy (53 mg/dl vs. 70 mg/dl at 1 year), and the trial reaffirmed the LDL-C hypothesis that reducing LDL-C prevents CV events.

A large meta-analysis using IVUS plaque progression and/or regression studies demonstrated a direct relationship between the burden of coronary atherosclerosis, its progression, and adverse CV events ([14](#)). Our PRECISE-IVUS trial confirmed noninferiority and superiority of coronary plaque regression using the combination of atorvastatin/ezetimibe over atorvastatin alone. Therefore, the clinical event risk reduction in the IMPROVE-IT trial might be derived from the suppression effect of coronary atherosclerotic development by dual lipid lowering. In addition, mean LDL-C levels were closely correlated with median change in PAV in several IVUS trials ([15-18](#)). With

FIGURE 4 Correlation Between Absolute Change in PAV and Biomarkers



The relationship between the absolute change in PAV and biomarkers at 9 to 12 months of follow-up is demonstrated with the low-density lipoprotein cholesterol (LDL-C) level in the (A) full study, (B) ACS, and (C) SAP cohorts, as well as with the percent change in the campesterol-to-cholesterol ratio in the (D) full study, (E) ACS, and (F) SAP cohorts. Abbreviations as in Figure 1.

regard to the lipid-lowering effects of a statin/ezetimibe combination, even in the present PRECISE-IVUS trial, the dual lipid-lowering strategy was associated with lower LDL-C levels at follow-up and greater reduction in LDL-C during the study compared with statin monotherapy, which is similar to previous studies (6,19). Our results reaffirmed the relationship between the achieved lower LDL-C level and coronary plaque regression. Conversely, because the study protocol demanded that participating physicians target LDL-C to <70 mg/dl, the higher achieved LDL-C levels in patients treated with atorvastatin alone demonstrated clinical limitations of statin monotherapy in lipid-lowering and antiatherosclerotic effects against coronary plaque.

Another possible mechanism underlying the clinical benefit obtained by dual lipid lowering was the suppression of the compensatory enhancement of cholesterol absorption. The DEBATE (Drugs and Evidence-Based Medicine in the Elderly) study showed that mortality increased with increasing

levels of the cholesterol absorption marker, the cholestanol-to-cholesterol ratio (20). The present study found a positive correlation between the suppression of cholesterol absorption markers and coronary plaque regression, which reconfirmed the inhibitory effect of ezetimibe added to statin-induced accelerated cholesterol absorption markers. Furthermore, a previous optical coherence tomography study suggested plaque stabilization using a fluvastatin/ezetimibe combination, which showed a thickened fibrous cap that protected lipid-rich plaque in patients treated by dual lipid lowering compared with fluvastatin monotherapy (19).

As described previously, a close relationship exists between the achieved LDL-C level and coronary plaque regression, and the cutoff point when coronary atherosclerotic development turned from plaque progression to regression was an achieved LDL-C level at approximately 75 mg/dl (15). The achieved LDL-C level was significantly suppressed in patients with plaque regression compared with patients with plaque

progression (Table 4). A systematic review demonstrated that statin/ezetimibe combination therapy (especially with strong statins) could help attain the previously recommended strict LDL-C goals of <70 mg/dl (21). Although the new cholesterol treatment guidelines released by the ACC/AHA emphasizes matching the intensity of statin treatment to the level of atherosclerotic CV disease risk (“fire and forget” concept), which replaces the old paradigm of pursuing LDL-C goals (“treat to target” concept) (4), our positive results from the PRECISE-IVUS trial could lead to an early re-evaluation of the new ACC/AHA lipid management guidelines that endorses statins as the only recommended drugs for treating cholesterol-related CV risk. Also, our results provide evidence that supports the concept that ezetimibe added to standard statin therapy can be effective in patients who are unable to tolerate high-dose statins, those who may better tolerate a combination of low-dose statin plus ezetimibe, and those who cannot achieve adequate LDL-C lowering despite high-dose statin use.

Finally, previous studies showed that statin-induced coronary plaque regression appeared to be more prominent in patients with ACS (–13.1% to –18.1% in a median percentage of change in TAV) (10,22) than in patients with SAP (–0.4% to –6.8% in a median percentage of change in TAV) (15,17). Although the association between coronary plaque regression induced by statin therapy and patients’ clinical presentation (stable or unstable status) has been speculated, this association has not been validated by a study with a prospective randomized design. Our findings from PRECISE-IVUS confirm that the correlated plaque regression with lower achieved LDL-C level was especially evident in the ACS cohort, which suggests the potential correlation between stronger plaque regression and the acute unstable presentation of vulnerable patients. Therefore, the combination of statin/ezetimibe might be a particularly effective treatment option for vulnerable patients with a high risk of CAD (e.g., such as individuals with high baseline LDL-C values, diabetes, established CV disease, or familial hypercholesterolemia).

STUDY LIMITATIONS. First, the present analysis compared coronary plaque in patients treated with standard statin monotherapy as a control cohort, because it was not ethically acceptable to measure disease progression and/or regression in placebo-treated patients. Second, because the trial involved patients who underwent PCI, it remains unknown whether our findings could be applied to primary prevention in patients without documented CAD. Third, this study used IVUS imaging to examine disease

progression and/or regression, but newer analytical methods might permit better characterization of coronary plaque components. However, case samples that could be evaluated by IVUS-derived tissue characterization software were limited. Fourth, it was reported that thrombus, which is frequently seen in culprit lesions of ACS, could not be detected by a traditional IVUS system with high sensitivity and specificity. Therefore, strict attention was paid to exclude thrombus in this study. Fifth, although expert consensus recommends that investigators acquire a segment that is as long as possible because of the increase in variability when short segments are analyzed, the analyzed segment length was relatively short in our study because IVUS examination of non-PCI vessels tended to be avoided for ethical and safety reasons, and the target segment to be monitored was determined in a non-PCI site (>5 mm proximal or distal to the PCI site) with reproducible fiducial indexes.

CONCLUSIONS

Among Japanese patients who underwent PCI, aggressive lipid-lowering with dual inhibition of cholesterol synthesis and absorption produced stronger coronary plaque regression compared with sole inhibition of the cholesterol biosynthetic pathway. Combination therapy with statin plus ezetimibe might thus be a promising lipid-lowering option for high-risk patients.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Kenichi Tsujita, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan. E-mail: tsujita@kumamoto-u.ac.jp.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Combination therapy with atorvastatin plus ezetimibe was associated with greater coronary plaque regression than atorvastatin alone in patients who underwent PCI.

TRANSLATIONAL OUTLOOK:

Additional studies are needed to ascertain the mechanism by which ezetimibe accelerates plaque regression in this situation compared with statin monotherapy.

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KEY WORDS HMG-CoA reductase inhibitors, intravascular ultrasound

APPENDIX For a complete list of the members of the PRECISE-IVUS study and a supplemental table, please see the online version of this article.